Total Synthesis of (*S*)-(+)-Imperanene. Effective Use of Regio- and Enantioselective Intramolecular Carbon−Hydrogen Insertion Reactions Catalyzed by Chiral Dirhodium(II) Carboxamidates

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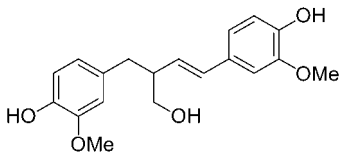
The total synthesis of (*S*)-(+)-imperanene, a natural product found in Chinese medicine, has been completed in 12 steps from a commercially available cinnamic acid. The key step is highly enantioselective carbon−hydrogen insertion from a diazoacetate using a chiral dirhodium(II) carboxamidate catalyst. An elimination process essential to the construction has been optimized to avoid intramolecular Friedel−Crafts alkylation.

(+)-Imperanene (**1**) is a novel phenolic compound that has been isolated from *Imperata cylindrica*.[1] The rhizomes of *I. cylindrica* have been used in Chinese medicine as diuretic and antiinflammatory agents,[2a] and imperanene has been shown to have platelet aggregation inhibitory activity. When we first submitted this manuscript, there was then no report of the total synthesis of this compound, and its absolute configuration had not been determined. A recent publication has reported its enantioselective synthesis using a chiral auxiliary,[2b] but concerns regarding the initially reported optical rotation were not resolved.



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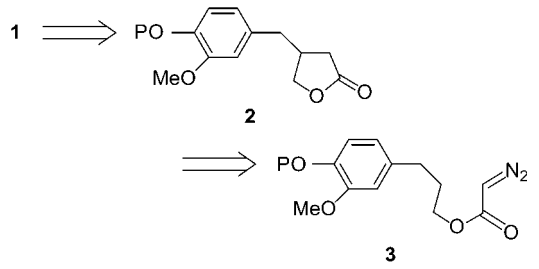
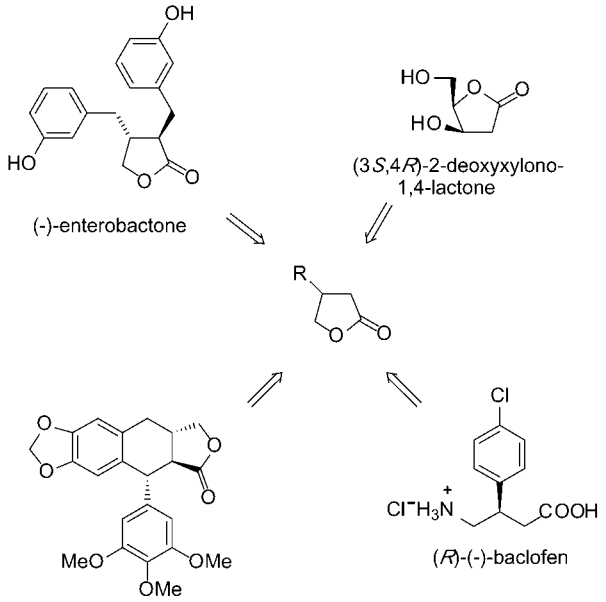
We envisioned a synthetic strategy to imperanene through lactone **2** (P = protective group) accessible by a variety of methodologies,[3] the most advantageous on the basis of enantiocontrol and number of reaction steps being the carbon−hydrogen insertion pathway from diazoacetate **3**.[4] This methodology effects virtually regiospecific carbene insertion into an unactivated C−H bond four atoms removed from the carbon center and has been demonstrated to be effective for the highly enantioselective syntheses of lignans[5] ranging from enterolactone and arctigenin to isodeoxypodophyllotoxin[4] and for the construction of nearly optically pure forms of 2-deoxyxylono-1,4-lactone[6] and baclofen.[7] Both enantiomeric forms are available by this methodology.





Although chiral dirhodium(II) carboxamidates **4**−**7** have been used with varying success in C−H insertion reactions of diazoacetates,[8,9] only the Rh_2(MPPIM)$_4$ cata-

(1) Matsumaga, K.; Shibuya, M.; Ohizumim, Y. *J. Nat. Prod.* **1995**, *58*, 138.

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(6) Doyle, M. P.; Tedrow, J. S.; Dyatkin, A. B.; Spaans, C. J.; Ene, D. G. *J. Org. Chem.* **1999**, *64*, 8907.

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(8) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998; Chapter 3. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

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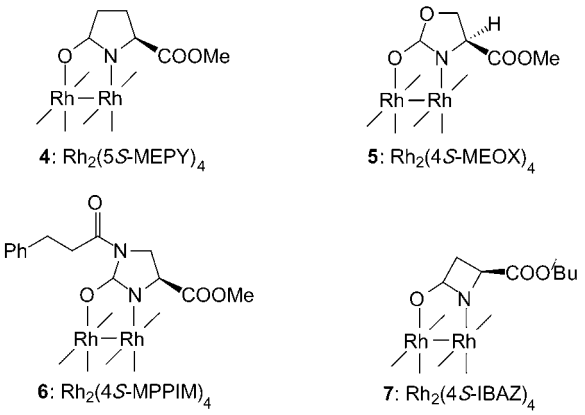
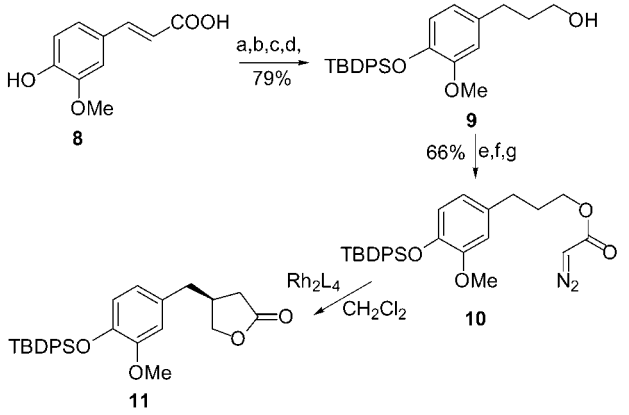
lysts[10] have led to greater than 20:1 enantioselection. This is due primarily to the increased steric interactions of



ligands with the reacting carbene, which restrict available conformations and direct product formation. Both enantiomeric forms of the 3-benzyl-γ-butyrolactone product are available via this methodology; $Rh_2(4S\text{-MPPIM})_4$ forms the *S*-configured lactone product, whereas $Rh_2(4R\text{-MPPIM})_4$ yields the *R*-enantiomer in all cases examined thus far.

The synthesis of **3** (P = ^{t}BuPh$_2$Si) employed standard methods (Scheme 1)[11] and use of *tert*-butyldiphenylsilyl

Scheme 1[a]



[a] (a) H_2, 10% Pd/C; (b) MeOH, H^+; (c) TBDPSCl/imidazole/DMF; (d) $LiAlH_4$, THF; (e) diketene/Et_3N; (f) MsN_3 Et_3N; (g) LiOH/H2O/THF.

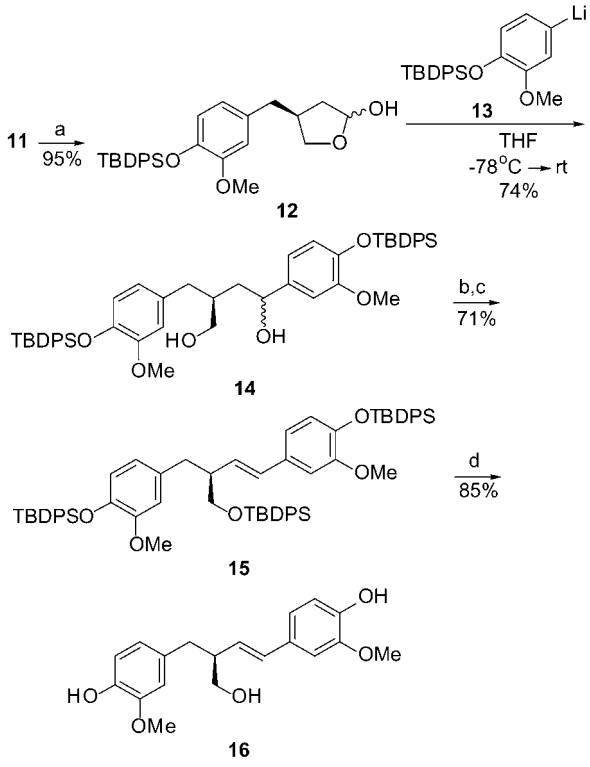
TBDPS as the phenolic protective group.[12] The benzyl ether was used in model studies instead of TBDPS, but the difficulties of its deprotection in the presence of a carbon−carbon double bond made this approach unrealistic in the overall synthetic scheme. The synthesis of **10** from **9** followed well-established procedures.[13] Catalytic intramolecular C−H insertion occurred cleanly and in good yield with $Rh_2(4S\text{-MPPIM})_4$; this catalyst gave the highest enantiomeric excess of **11** (93%) without evidence of either β- or δ-lactone products. The influence of catalyst

Table 1. Yield and % ee Values for the Synthesis of 11 from 10 by Catalytic Intramolecular C−H Insertion with 4−7[a]

catalyst	yield **11**, %[b]	ee, %[c]
$Rh_2(4S\text{-MPPIM})_4$ (**6**)	68	93
$Rh_2(5R\text{-MEPY})_4$ (**ent-4**)	51	(67)[d]
$Rh_2(4S\text{-MEOX})_4$ (**5**)	37	36
$Rh_2(4S\text{-IBAZ})_4$ (**7**)	40	42

[a] Reactions performed in refluxing CH_2Cl_2 containing 1.0 mol % of catalyst by 5-h addition of **10** (2.0 mmol) in 2 mL of CH_2Cl_2. [b] Weight yield after chromatography. [c] Analysis by HPLC on a Chiralpak OD column (98:2 hexane/^{i}PrOH). [d] Enantiomer of **11** was dominant.

Scheme 2[a]



[a] (a) DIBAL-H; (b) TDBPSCl/DMF/imidazole; (c) MsCl/DBU in PhCl, reflux; (d) TBAF.

on the yield and % ee of **11** is presented in Table 1. Significantly lower product yields and selectivities were observed with catalysts other than $Rh_2(4S\text{-MPPIM})_4$. With the benzyl ether corresponding to **10** (Bn instead of TBDPS), use of $Rh_2(4S\text{-MPPIM})_4$ gave the lactone product corresponding to **11** with 96% ee.

Lactone **11** having the *S*-configuration[4] was reduced[14] and then alkylated with aryllithium **13**[12] to produce a nearly 50:50 diastereomeric diol mixture (**14**, Scheme 2). The primary alcohol was selectively protected with TBDPSCl (95% yield)[15] and then treated with MsCl/DBU in refluxing chlorobenzene[16] to produce **15** exclusively as the *E*-isomer. Deprotection of **15** with tetrabutylammonium fluoride gave **16**, whose spectral properties were

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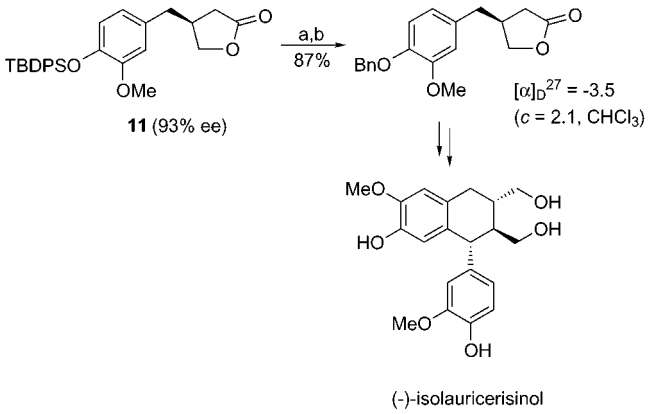
Scheme 3[a]



[a] (a) TBAF (1.1 equiv, 0 °C, 20 min); (b) BnBr, 2 equiv, rt, 2 h).

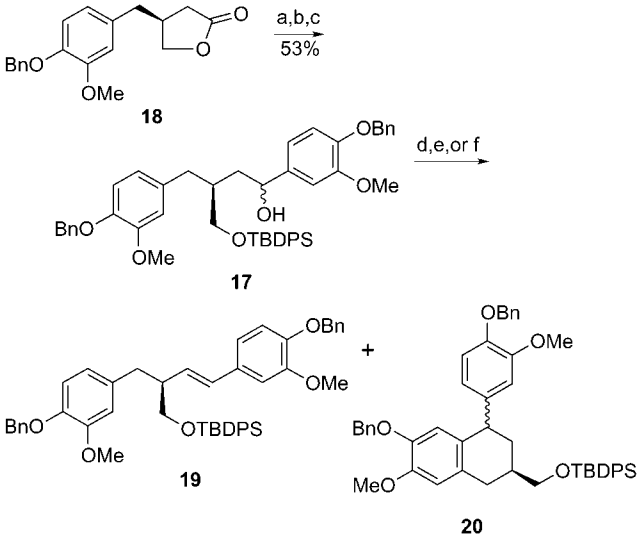
identical to those reported for (+)-imperanene.[1] The observed rotation of **16** was +103° for a compound that was 93% ee by the methodology employed. Since the reported rotation for **1** was +700°,[1] further characterization of the synthetic material was performed. First of all, the rotation of **16** was invariant with concentration over a factor of 10. Second, conversion of **16** to the trifluoroacetate ester of the primary alcohol (TFAA in pyridine) allowed HPLC determination of the enantiomeric composition, on a 25-cm Chiralpak OD column [14.7 min for (*R*)-**1** and 21.7 min for (*S*)-**1**], and this analysis confirmed the 93% ee of **16**. Furthermore, removal of the TBDPS group from **11** and replacement with a benzyl group (Scheme 3) allowed correlation with the lactone (*R*-isomer, $[\alpha]_D = +3.7°$ for 96% ee) from which isolauricerisinol of known configuration has been produced.[4] Consequently, on the basis of these results and on the configurational preference for (*S*)-**11** with the use of Rh_2(4*S*-MPPIM)$_4$ on diazoacetates directly related to **10**,[4] we can assign the absolute configuration of **1** as *S*.

When excess TBAF is used, the yield-limiting step in Scheme 2 is that for deprotection, and the cause is the removal of TBDPS from the primary alkoxide. The phenolic TBDPS comes off rapidly and quantitatively with TBAF within 30 min at 0 °C. The remaining protective group requires 12 h at room temperature using a solution that contains an equivalent amount of TBAF. Excess reagent lowers product yield.

The conditions employed for the elimination reaction used for the preparation of **15** were established through laborious investigations with its dibenzyl ether analogue **17**, prepared from lactone **18** (Scheme 4) through a set of steps similar to that employed for the synthesis of **15**. Use of relatively mild conditions (condition d)[16] resulted in an unexpected preponderance of the Friedel−Crafts alkylation product **20**. With the more reactive MsCl and DBU in refluxing THF, the proportion of elimination product **19** increased; and when the same reaction was performed in refluxing chlorobenzene, elimination occurred in preference to Friedel−Crafts alkylation. When these same conditions were applied to the TBDPS-protected **14** (Scheme 2), elimination was predominant and the Friedel−Crafts alkylation product **21** was only a minor constituent of the reaction mixture (**16**:**21** = 86:14).

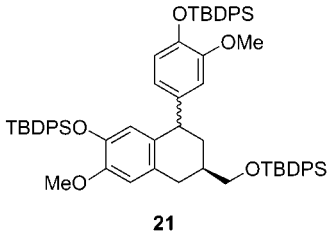
In efforts to prepare **21** as the exclusive product, neat

Scheme 4[a]

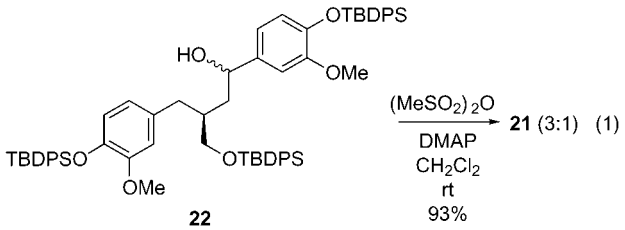


[a] (a) DIBAL-H; (b) ArMgBr/Et_2O; (c) TBDPSCl/imidazole/DMF; (d) $(MeSO_2)_2O$/DMAP/CH_2Cl_2, reflux → **19**:**20** = 9:91; (e) $MeSO_2Cl$/DBU/THF, reflux → **19**:**20** = 38:62; (f) $MeSO_2Cl$/DBU/PhCl, reflux → **19**:**20** = 71:29.

trifluoroacetic acid was recommended,[17] but its use did not form **21** from **22** as anticipated; a complex mixture of materials was formed that was not further analyzed.



Optimum conditions were realized with the use of methanesulfonic anhydride and DMAP at room temperature (eq 1), from which **21** was obtained as a mixture of two diastereoisomers (3:1). The contrast between these conditions and those used to prepare the elimination product **15** is noteworthy.



(*S*)−(+)-Imperanene has been synthesized in 12 steps and approximately 16% overall yield. Improvements in the overall scheme that will give higher yields are transparent, but the core reaction, enantioselective C−H insertion, is optimized.

Experimental Section

General. ^1H NMR (250, 500, or 600 MHz) and ^{13}C NMR (62.5, 125, or 150 MHz) spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard, Me_4Si (TMS). Mass spectra were obtained using electron ionization on a quadruapole instrument. Elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ. Anhydrous THF

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was distilled over sodium/benzophenone ketyl, and dichloromethane was distilled over calcium hydride. Methanesulfonyl azide (MsN_3) was prepared by reaction of methanesulfonyl chloride with sodium azide[18] and was not distilled. Dirhodium(II) catalysts were prepared as previously described.[19−22] Unless otherwise stated, all chemicals were used without further purification.

3-(4-Hydroxy-3-methoxyphenyl)propionic Acid. A solution of ferulic acid **8** (15.0 g, 77.2 mmol) in 1.0 N aqueous sodium hydroxide (155.0 mL, 155.0 mmol) containing 100 mg of 10% Pd/C was hydrogenated under 30 bar of hydrogen pressure at room temperature for 12 h. The catalyst was filtered though Celite, sodium hydroxide (155.0 mL, 155.0 mmol) containing 100 mg of 10% Pd/C was hydrogenated under 30 bar of hydrogen pressure, and the filtrate was acidified with concentrated H_2SO_4 to pH = 2. The water solution was then extracted with CH_2Cl_2 (4 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give hydroferulic acid as a white solid that was identical to that previously reported (14.8 g, 97% yield):[23] ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H), 6.72−6.68 (comp, 2H), 3.86 (s, 3H), 2.89 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9, 146.4, 144.1, 132.1, 120.9, 114.4, 111.0, 55.9, 35.9, 30.3.

Methyl 3-(4-Hydroxy-3-methoxyphenyl)propionate.[23] A solution of hydroferulic acid (14.8 g, 75.7 mmol) in 150 mL of MeOH containing 0.2 mL of concentrated H_2SO_4 was refluxed overnight. Methanol was evaporated, and the residue was dissolved in 150 mL of CH_2Cl_2 and then washed with H_2O and brine. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give methyl hydroferulate as a liquid (15.5 g, 97% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (d, J = 7.8 Hz, 1H), 6.71−6.65 (comp, 2H), 5.50 (br s, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 2.88 (t, J = 7.8 Hz, 2H), 2.60 (t, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.4, 146.4, 144.0, 132.4, 120.8, 114.3, 110.9, 55.8, 51.5, 36.1, 30.1.

3-[4-(*tert*-Butyldiphenylsilanoxy)-3-methoxyphenyl]-propan-1-ol (9). To an anhydrous DMF (4 mL) solution of methyl hydroferulate (2.1 g, 10.0 mmol) and imidazole (0.82 g, 12 mmol) was added TBDPSCl (2.7 g, 10.0 mmol) at 0 °C for 10 min. The reaction mixture was warmed to room temperature, and stirring was continued for 50 h. Ethyl acetate (50 mL) was added, and the resulting mixture was washed with 1 M HCl (20 mL), H_2O (20 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated to give crude methyl TBDPS-hydroferulate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.32 (comp, 10H), 6.65 (d, J = 1.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 2.84 (t, J = 7.5 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 1.10 (s, 9H). To a THF (20 mL) solution of the crude product was added a 1 M THF solution of $LiAlH_4$ (17.0 mL, 17.0 mmol) at −78 °C during 30 min. Stirring was continued for an additional 2 h. Methanol was added to quench the reaction until no hydrogen gas was observed. To the mixture was then added 1 M HCl (50 mL) and ethyl acetate (100 mL). The organic layer was washed with 1 M HCl (30 mL), H_2O (50 mL), and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 2:1) to give alcohol **9** as a viscous oil (3.4 g, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.69 (comp, 4H), 7.41−7.36 (comp, 2H), 7.35−7.31 (comp, 4H), 6.62 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.46 (dd, J = 8.0, 2.0 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H), 3.54 (s, 3H), 2.56 (t, J = 7.5 Hz, 2H), 1.81 (tt, J = 7.5, 6.5 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 143.1, 135.4, 135.0, 133.7, 129.5, 127.4, 120.2, 119.9, 112.7, 62.3, 55.4, 34.2, 31.7, 26.7, 19.7.

3-[4-(*tert*-Butyldiphenylsilanoxy)-3-methoxyphenyl]-propyl Diazoacetate (10). A solution of alcohol **9** (2.1 g, 5.0 mmol) in 10 mL of CH_2Cl_2 was treated with triethylamine (0.1 g, 1.0 mmol) and diketene (0.50 g, 6.0 mmol) at 0 °C. The solution was allowed to warm to room temperature, and stirring was continued for 16 h. The reaction mixture was then cooled to 0 °C. Triethylamine (0.7 g, 7.0 mmol) was added, followed by addition of MsN_3 (0.67 g, 5.5 mmol). The reaction solution was allowed to warm to room temperature, and stirring was continued for 24 h, after which the solvent was removed under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate and then washed with H_2O (50 mL) and brine (50 mL). After drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The crude diazoacetoacetate was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 10:1). To the THF (10 mL) solution of the diazoacetoacetate was added LiOH hydrate (2.1 g, 50.0 mmol) in H_2O (10 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 0.5 h until the cleavage was complete. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, and the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes/ethyl acetate = 10:1) yielded diazoacetate **10** as a yellow oil (1.6 g, 66% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80−7.73 (comp, 4H), 7.45−7.34 (comp, 6H), 6.68 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 7.8, 2.4 Hz, 1H), 4.73 (s, 1H), 4.17 (t, J = 6.6 Hz, 2H), 3.59 (s, 3H), 2.59 (t, J = 7.8 Hz, 2H), 1.93 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 143.2, 135.3, 134.2, 133.6, 129.4, 127.4, 120.1, 120.0, 112.6, 64.0, 55.3, 46.0, 31.5, 30.3, 26.6, 19.7. Anal. Calcd for $C_{28}H_{32}O_4N_2Si$: C, 68.82; H, 6.60; N, 5.73. Found: C, 68.94; H, 6.42; N, 5.64.

(4*S*)-(−)-4-{2-[4-(*tert*-Butyldiphenylsilanyloxy)-3-methoxyphenyl]ethyl}dihydrofuran-2-one (11). To a refluxing CH_2Cl_2 (40 mL) solution of Rh_2(4*S*-MPPIM)$_4$ (28 mg, 1.0 mol %) was added diazo compound **10** (0.98 g, 2.0 mmol) in 10 mL of CH_2Cl_2 during 5 h via a syringe pump. The solvent was evaporated, and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 10:1) to give γ-lactone **11** as a viscous oil with 93% ee (0.63 g, 68% yield): $[\alpha]^{25}_D = -0.7°$ (c = 0.5, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.8, 1.2 Hz, 4H), 7.39 (tt, J = 7.8, 1.2 Hz, 2H), 7.33 (t, J = 7.8 Hz, 4H), 6.64 (d, J = 7.8 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 7.8, 2.4 Hz, 1H), 4.25 (dd, J = 9.0, 7.2 Hz, 1H), 3.95 (dd, J = 9.0, 6.6 Hz, 1H), 3.54 (s, 3H), 2.74 (m, 1H), 2.64 (dd, J = 13.8, 7.8 Hz, 1H), 2.60 (dd, J = 13.8, 8.4 Hz, 1H), 2.53 (dd, J = 17.4, 8.4 Hz, 1H), 2.21 (dd, J = 17.4, 7.2 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.8, 150.6, 143.9, 135.4, 133.5, 131.4, 129.6, 127.4, 120.5, 120.4, 112.7, 72.6, 55.4, 38.5, 37.2, 34.2, 26.0, 19.7; HRMS calcd for $C_{28}H_{32}O_4SiCs$ ($M + Cs^+$) 593.1142, found 593.1265. Enantiomeric excess was found by HPLC using a 25-cm Chiralpak OD column with hexane/*i*-PrOH eleunt of 98:2 (0.8 mL/min): t_R (minor) 53.6 min, t_R (major) 58.1 min.

(2*RS*)-(4*S*)-4-{2-[4-(*tert*-Butyldiphenylsilanyloxy)-3-methoxyphenyl]ethyl}tetrahydrofuran-2-ol (12). To an anhydrous CH_2Cl_2 (15 mL) solution of γ-lactone **11** (0.46 g, 1.0 mmol) was added 1.5 M DIBAL-H in toluene (0.67 mL, 1.0 mmol) at −78 °C during 30 min. Stirring was continued at the same temperature for an additional 2 h. Methanol was added to quench the reaction. The mixture was allowed to warm to room temperature, and 30 mL of CH_2Cl_2 was added. The CH_2Cl_2 solution was washed with 1 N HCl (2 × 20 mL), H_2O (20 mL), and brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 5:1) to give **12** as a viscous oil (0.44 g, 95% yield): ^{1}H NMR (600 MHz, $CDCl_3$) major isomer δ 7.69 (d, J = 7.2 Hz, 4H), 7.37 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz,

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4H), 6.62 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 6.42 (dd, J = 8.4, 1.8 Hz, 1H), 5.51 (m, 1H), 4.01 (t, J = 7.8 Hz, 1H), 3.52 (s, 3H), 3.48 (t, J = 7.8 Hz, 1H), 3.07 (br d, J = 3.6 Hz, 1H), 2.54 (dd, J = 13.8, 7.2 Hz, 1H), 2.50 (dd, J = 13.8, 8.4 Hz, 1H), 2.68 (m, 1H), 1.93 (dd, J = 13.2, 7.2 Hz, 1H), 1.63 (ddd, J = 13.2, 9.0, 5.4 Hz, 1H), 1.11 (s, 9H); minor isomer δ 7.69 (d, J = 7.2 Hz, 4H), 7.37 (t, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 4H), 6.62 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.44 (dd, J = 8.4, 1.8 Hz, 1H), 5.51 (m, 1H), 3.83 (t, J = 7.8 Hz, 1H), 3.66 (t, J = 7.8 Hz, 1H), 3.52 (s, 3H), 3.22 (br d, J = 3.6 Hz, 1H), 2.66 (dd, J = 13.8, 7.8 Hz, 1H), 2.62 (dd, J = 13.8, 7.8 Hz, 1H), 2.41 (m, 1H), 2.16 (ddd, J = 13.2, 7.2, 6.0 Hz, 1H), 1.54 (ddd, J = 13.2, 7.2, 4.2 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) major isomer δ 150.3, 143.4, 135.4, 133.7, 133.6, 129.5, 127.4, 120.5, 120.0, 112.8, 98.7, 72.2, 55.3, 39.7, 39.1, 38.8, 26.7, 19.7; minor isomer δ 150.3, 143.4, 135.4, 133.9, 133.7, 129.5, 127.4, 120.4, 120.0, 112.8, 99.1, 71.9, 55.3, 40.4, 39.5, 38.9, 26.7, 19.7; HRMS calcd for $C_{28}H_{34}O_4SiCs$ ($M + Cs^+$) 595.1281, found 595.1265.

4-Bromo-2-methoxyphenol.[24] To a 100-mL three-necked round-bottom flask containing 20 mL of carbon disulfide was added guaiacol (12.6 g, 0.100 mol). A mixture of bromine (16.8 g, 0.105 mol) in 5 mL of CS_2 was added dropwise to the solution (5 drops/min) by an addition funnel. The solution was stirred at 0 °C for 18 h, then washed with water (3 × 50 mL) and brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a viscous liquid that was identical to that previously reported (18.27 g, 90% yield):[25] ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (dd, J = 6.0 Hz, 2.5 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 3.80 (s, 3H), 5.75 (s, 1H); ^{13}C NMR (125 MHz) δ 147.1, 144.7, 124.0, 115.7, 114.0, 111.4. 56.0.

4-(*tert*-Butyldiphenylsilanoxy)-3-methoxybromobenzene. To a round-bottom flask containing 2-bromo-5-methoxy phenol (3.66 g, 18 mmol) and imidazole (1.46 g, 22 mmol) was added 5 mL of DMF. The resulting solution was stirred at room temperature under argon for 10 min, then *tert*-butylchlorodiphenylsilane (4.95 g, 18 mmol) was added, and the resulting solution was allowed to stir for 52 h. Ethyl acetate was added, then washed with water and brine, and dried over anhydrous sodium sulfate. The solution was concentrated to give the title product as a viscous liquid (7.73 g, 97% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72−7.70 (comp, 4H), 7.42−7.34 (comp, 6H), 6.87 (d, J = 2.5 Hz, 1H), 6.77 (dd, J = 8.5 Hz, 2.5 Hz, 1 H), 6.59 (d, J = 8.5 Hz, 1H), 3.55 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (125 MHz) δ 151.27, 144.30, 135.26, 133.13, 129.69, 127.53, 123.27, 121.22, 115.53, 113.20, 55.41, 26.57, 19.70.

(1*RS*)-(3*R*)-3-[4-(*tert*-Butyldiphenylsilanyloxy)-3-methoxybenzyl]-1-[4-(*tert*-butyldiphenylsilanyl-oxy)-3-methoxyphenyl]butane-1,4-diol (14). To a THF (20 mL) solution of 4-(*tert*-butyldiphenylsilanoxy)-3-methoxybromobenzene (1.33 g, 3.0 mmol) was added 1.7 M *t*-BuLi in hexanes (3.5 mL, 6.0 mmol) at −78 °C. Stirring was continued for 2 h. To the solution was added **12** (0.5 g, 1.08 mmol) in 5 mL of THF. The reaction mixture was allowed to warm to room temperature. After stirring for 12 h at room temperature, the reaction was quenched by addition of aqueous NH_4Cl. Solvent was evaporated under reduced pressure, H_2O (20 mL) was added, and the resulting mixture was extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 2:1) to give **14** as a viscous oil (0.66 g, 74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) an approximately 1:1 mixture of diastereomers δ 7.71−7.66 (comp, 8H), 7.37−7.26 (comp, 12H), 6.68 (br s, 1H), 6.61 (d, J = 8.0 Hz, 0.5H), 6.60 (d, J = 8.0 Hz, 0.5H), 6.59 (d, J = 8.0 Hz, 0.5H), 6.58 (d, J = 8.0 Hz, 0.5H), 6.50 (d, J = 2.0 Hz, 0.5H), 6.48−6.46 (comp, 1H), 6.45 (dd, J = 8.0, 2.0 Hz, 0.5H), 6.38 (dd, J = 8.0, 2.0 Hz, 0.5H), 6.35 (dd, J = 8.0, 2.0 Hz, 0.5H), 4.65 (dd, J = 8.0, 4.0 Hz, 0.5H), 4.43 (dd, J = 9.0, 3.5 Hz, 0.5H), 3.59 (dd, J = 11.0, 4.0 Hz, 0.5H), 3.53 (m, 0.5H), 3.50 (s, 1.5H), 3.49 (s, 1.5H), 3.47 (s, 1.5H), 3.45 (s, 1.5H), 3.40 (dd, J = 11.0, 6.0 Hz, 0.5H), 3.39 (dd, J = 9.5, 7.0 Hz, 0.5H), 2.49 (dd, J = 13.5, 7.5 Hz, 0.5H), 2.46 (dd, J = 14.0, 7.5 Hz, 0.5H), 2.41 (dd, J = 14.0, 7.5 Hz, 0.5H), 2.34 (dd, J = 13.5, 7.5 Hz, 0.5H), 1.91−1.59 (comp, 3H), 1.10 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) mixture of diastereomers δ 150.47(150.44), 150.3, 144.35(144.30), 143.3, 138.35(137.96), 135.3, 133.64(133.55), 133.48(133.42), 129.54-(129.50), 127.43(127.38), 120.99(120.91), 119.91(119.78), 117.7, 113.21(113.12), 109.76(109.65), 73.75(71.36), 66.07(65.29), 55.3, 42.29(41.45), 40.89(39.06), 38.61(37.40), 26.6, 19.7; HRMS calcd for $C_{51}H_{60}O_6Si_2Cs$ ($M + Cs^+$) 957.2983, found 957.2981.

(3*S*)-1,4-Bis[4-(*tert*-butyldiphenylsilanyloxy)-3-methoxyphenyl]-3-(*tert*-butyldiphenylsilanyl-oxymethyl)butan-1-ol. To a stirred DMF (5 mL) solution of diol **14** (120 mg, 0.15 mmol) and imidazole (21 mg, 0.30 mmol) was added TBDPSCl (49 mg, 0.18 mmol) at 0 °C. Stirring was continued until no starting material was left in the reaction mixture as determined by TLC. Ethyl acetate (20 mL) was added, and the resulting mixture was washed with 0.5 N HCl (10 mL), H_2O (10 mL), and brine (10 mL). After drying over anhydrous Na_2SO_4, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 50:1) to give the monoprotected diol as a viscous oil (155 mg, 98% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.67 (comp, 8H), 7.63−7.55 (comp, 4H), 7.40−7.25 (comp, 18H), 6.69 (d, J = 1.8 Hz, 0.5H), 6.63 (d, J = 1.8 Hz, 0.5H), 6.62 (d, J = 8.4 Hz, 0.5H), 6.60 (d, J = 8.4 Hz, 0.5H), 6.55 (d, J = 8.4 Hz, 0.5H), 6.46 (dd, J = 8.4, 1.8 Hz, 0.5H), 6.45−6.43 (comp, 1H), 6.37 (dd, J = 8.4, 1.8 Hz, 0.5H), 6.30 (dd, J = 8.4, 1.8 Hz, 1H), 4.55 (m, 0.5H), 4.35 (m, 0.5H), 3.56−3.47 (comp, 2H), 3.48 (s, 1.5H), 3.47 (s, 1.5H), 3.41 (s, 1.5H), 3.40 (s, 1.5H), 2.55 (dd, J = 13.2, 7.2 Hz, 0.5H), 2.54 (dd, J = 13.8, 7.2 Hz, 0.5H), 2.45 (dd, J = 13.2, 6.0 Hz, 0.5H), 2.36 (dd, J = 13.8, 7.8 Hz, 0.5H), 1.86−1.76 (comp, 1H), 1.76−1.69 (comp, 1.5H), 1.61−1.57 (comp, 0.5H), 1.11 (s, 4.5H), 1.10 (s, 9H), 1.06 (s, 9H), 1.05 (s, 4.5H); ^{13}C NMR (150 MHz, $CDCl_3$) for mixture of diastereomers δ 150.41(150.39), 150.1, 144.20(144.19), 143.11(143.07), 138.2, 135.6, 135.5, 135.4, 135.3, 133.8, 133.71(133.69), 133.63(133.60), 133.58(133.52), 133.40(133.36), 133.33(133.31), 129.7, 129.62(129.61), 129.54(129.52), 129.47(129.46), 127.6, 127.42(127.37), 121.0, 119.8, 119.71(119.68), 118.03(117.90), 113.28(113.20), 109.91(109.80), 72.93(71.78), 66.66(66.63), 60.37(55.20), 55.22(55.17), 41.43(40.96), 40.09(39.02), 37.81(37.64), 26.94(26.65), 26.64(26.54), 20.97(18.97), 19.73(19.72), 19.25(19.23).

(3*S*)-(+)-1,4-Bis[4-(*tert*-butyldiphenylsilanyloxy)-3-methoxyphenyl]-3-(*tert*-butyldiphenylsilanyl-oxymethyl)but-1-ene (15). To a refluxing chlorobenzene (5 mL) solution of the monoprotected diol (0.40 g, 0.375 mmol) and DBU (0.56 g, 3.75 mmol) was added methanesulfonyl chloride (0.21 g, 1.88 mmol) in 5 mL of chlorobenzene during 2 h via syringe pump. To the reaction mixture was added 20 mL of ethyl acetate, which was then washed with H_2O (15 mL), saturated NH_4Cl (15 mL), and brine. After drying over anhydrous Na_2SO_4, solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 99:1) to give olefin **15** as a solid (280 mg, 61% yield + 10% **21**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56−7.51 (comp, 12H), 7.41−7.22 (comp, 18H), 6.69 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 6.52 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 6.10 (d, J = 15.6 Hz, 1H), 5.86 (dd, J = 15.6, 8.4 Hz, 1H), 3.62−3.55 (comp, 2H), 3.53 (s, 3H), 3.41 (s, 3H), 2.84 (dd, J = 13.2, 6.0 Hz, 1H), 2.58 (dd, J = 13.2, 7.2 Hz, 1H), 2.52−2.47 (comp, 1H), 1.11 (s, 9H), 1.09 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.4, 150.0, 144.4, 143.1, 135.6, 135.4, 135.3, 133.8, 133.7, 133.6, 133.5, 131.5, 130.5, 129.6, 129.5, 129.4, 129.3, 127.6, 127.5, 127.4, 121.2, 120.0, 119.8, 118.7, 113.6, 109.7, 66.1, 55.3, 55.2, 47.1, 37.2, 26.9, 26.7, 19.7, 19.3; HRMS calcd for $C_{67}H_{76}Si_3O_5$ (M^+) 1044.5001, found 1044.5038. HPLC analysis on a 25 cm Chiralpak OD column with hexane: *i*-PrOH of 90:10 (1.0 mL/min): t_R (*R*-isomer) 20.5 min, t_R (*S*-isomer) 25.4 min.

Imperanene (16). To a 1.0 mL THF solution of **11** (112

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mg, 0.107 mmol) was added 1.0 M TBAF in THF (0.37 mL, 0.37 mmol) with stirring. After 12 h at room temperature, 20 mL of ethyl ether was added, and the organic solution was saturated with NH_4Cl solution (1.0 mL), H_2O (5 mL), and brine (5 mL). After drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 4:1) to give **16** as a colorless oil (30 mg, 85% yield): $[\alpha]^{25}_D = +103°$ ($c = 1.7$, $CHCl_3$), +97° ($c = 0.68$, $CHCl_3$), +96° ($c = 0.14$, $CHCl_3$); note that {[3(180°) + 103]/0.93} = 691, which is very close to the reported $[\alpha]_D$ of +700°, but we see no justification for adding 3(180°); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86−6.84 (comp, 3H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.70−6.67 (comp, 2H), 6.35 (d, $J = 16.2$ Hz, 1H), 5.92 (dd, $J = 16.2$, 8.4 Hz, 1H), 5.59 (s, 1H), 5.47 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.67 (dd, $J = 10.2$, 4.5 Hz, 1H), 3.56 (dd, $J = 10.2$, 7.8 Hz, 1H), 2.74 (dd, $J = 13.2$, 7.2 Hz, 1H), 2.69 (dd, $J = 13.2$, 7.2 Hz, 1H), 2.66−2.61 (comp, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.6, 146.3, 145.3, 143.9, 132.2, 131.5, 129.7, 128.4, 121.8, 119.7, 114.4, 114.1, 111.7, 108.2, 65.2, 55.9, 55.8, 47.6, 37.7; HRMS calcd for $C_{19}H_{22}O_5$ (M^+) 330.1467, found 330.1469.

7-(*tert*-Butyldiphenylsilanyloxy)-1-[4-(*tert*-butyldiphenylsilanyloxy)-3-methoxyphenyl]-3-(*tert*-butyl-diphenylsilanyloxymethyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (21). To an oven-dried vial was added DMAP (2.9 mg, 0.024 mmol), methanesulfonic anhydride (14.2 mg, 0.08 mmol), **22** (20 mg, 0.019 mmol), and 1 mL of anhydrous dichloromethane, and the solution was allowed to stir for 4 h. The resulting solution was subjected to column chromatography on silica gel (hexanes/ethyl acetate = 9:1) to give **21** as a viscous oil in 93% yield. NMR analyses indicated the presence of two isomers for **21** in a ratio of 3:1 and only a trace amount of elimination product **15** (1:50): ^{1}H NMR (500 MHz, $CDCl_3$) major isomer δ 7.77−7.14 (comp, 30H), 6.50 (d, $J = 8.0$ Hz, 1H), 6.46 (s, 1H), 6.32 (d, $J = 2.0$ Hz, 1H), 6.19 (dd, $J = 2.0$, 8.0 Hz, 1H), 6.15 (s, 1H), 3.63−3.55 (comp, 2H), 3.54 (s, 3H), 3.39 (s, 3H), 2.76 (dd, $J = 3.5$, 16.0 Hz, 1H), 2.52 (dd, $J = 12.0$, 16.0 Hz, 1H) 2.01−1.95 (comp, 2H), 1.40−1.20 (comp, 2H), 1.13 (S, 9H), 1.04 (S, 9H), 1.00 (S, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1, 148.5, 143.0, 142.8, 140.0, 136.0−135.3 (comp), 134.0−133.6 (comp), 132.2, 129.7−129.2 (comp), 120.7, 120.5, 119.6, 112.4, 112.3, 68.8, 55.5, 55.2, 45.7, 37.8, 37.0, 33.1, 26.9, 26.8, 26.7, 19.8, 19.7, 19.3; HRMS calcd for $C_{67}H_{75}SI_3O_5$ 1043.4922, found 1044.4954.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **11**, **12**, **14**, **16**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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